

Polymerization

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Thiol-Ene Step-Growth as a Versatile Route to Functional Polymers

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Abstract: A new use of the thiol-ene reaction to generate functional, redox-tunable polymers is described. To illustrate the versatility of this approach, tailored divinyl ether monomers were polymerized with triethylene glycol dithiol to yield polymers containing either a carbonate or zwitterionic phosphocholine within the polymer backbone. Similarly, dithioerythritol was polymerized with triethylene glycol divinyl ether to yield a polymer with pendant diols and show how functional groups can be designed into either the divinyl ether or dithiol monomer. Using the thioether functional group inherent to this polymerization, all three polymers were selectively and quantitatively oxidized to either sulfoxides or sulfones by treatment with dilute hydrogen peroxide or *m*CPBA, respectively. With these illustrative examples, it is shown that the thiol-ene polymerization is a broad-reaching method to access a class of new redox-active polymers which contain varied and dense functional-group compositions.

The union of synthetic organic chemistry and polymer science over the last 20 years has enabled the generation of new materials containing practically every chemical moiety conceivable.^[1] These advances promise new macromolecules with a very high degree of chemical functionality which is expected to rival nature's biopolymers such as proteins and DNA. Major progress in tailor-made polymers has been facilitated by new synthetic methods such as controlled radical polymerization^[2] and ring-opening metathesis polymerization (ROMP),^[3] as well as post-polymerization functionalization techniques such as so-called click reactions and activated ester methodologies.^[4] Despite the many differences among these strategies, most aim to generate new polymers with unprecedented degrees of functionalization and precise control over the placement of that functionality.

Many of these new methods have inherent limitations, with oxygen and water sensitivity being the most common. Moreover, because of the chain-growth nature of many polymerizations, functional groups are generally incorporated as side chains pendant to the polymer backbone. However, there are numerous opportunities, ranging from lithium ion conductivity by poly(ethylene oxide)^[5] to selective degradability of poly(lactic acid)^[6] where functional-group incorporation into the polymer backbone (main chain) is preferred. With these challenges in mind, we present the thiol-ene step-growth (TES) polymerization and demonstrate its ability to incorporate both main-chain functional groups (zwitterion,

carbonate) and pendant functional groups (diol) under ambient reaction conditions. This approach, which exploits the thiol-ene reaction to generate novel polymers, differs from the originally reported and most widely employed use of click reactions in the context of macromolecular science, that is, to functionalize existing materials.^[7,8] The ability to utilize both functional dienes and dithiols indicates a near infinite combination of possible polymer chemistries. Additionally, the thioethers within the resulting polymers are redox sensitive and can be controllably oxidized to obtain either a main-chain sulfoxide or sulfone, thus dramatically changing the polymer polarity and solubility properties.

In 1948, Marvel was one of the first to identify the thiol-ene addition as a possible route to the generation of macromolecules by considering the step-growth reaction of dienes and di-thiols as illustrated in Figure 1.^[9] Over the last six decades, there have been a few reports documenting the step-growth polymerization of single monomer styrenic thiols, α,ω -alkylene thiols, and two monomer systems utilizing aliphatic dithiols, diallyl ethers, and divinyl ethers.^[10–13] More recently, we demonstrated the polymerization of numerous dithiols and divinyl ethers, and the potential of these molecules to coordinate and conduct lithium cations as solid polymer electrolytes.^[14] By using this same concept, we also demonstrated linear multiblock copolymer formation through the reaction of telechelic dithiol and dinorbornene macromonomers.^[15,16] Herein, we report the TES polymerization of monomers to demonstrate its functional-group tolerance and spatial control, in addition to its redox responsive behavior. Through these examples, we show that TES polymerization is a viable candidate to generate novel, functional-group-dense macromolecules, and greatly improves access to new and interesting materials.

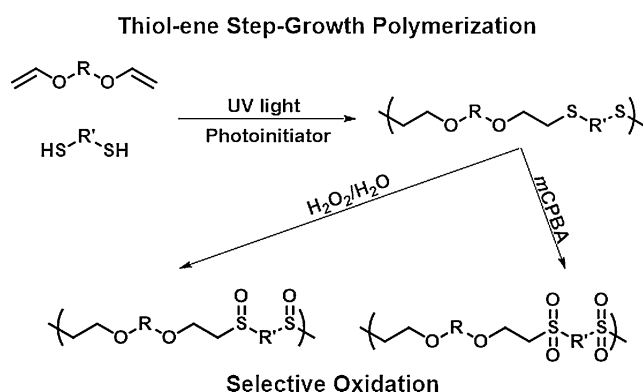


Figure 1. The thiol-ene step-growth polymerization using a dithiol and divinyl ether (top). Selective oxidation of TES polymers allows tuning of the hydrophilicity and solubility (bottom). *m*CPBA = *m*-chloroperoxybenzoic acid.

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To demonstrate the wide functional-group tolerance of both TES polymerizations and the subsequent oxidation reactions, we focus on three divinyl ether/dithiol monomer sets incorporating main- and side-chain functionalities (Scheme 1). A main-chain carbonate divinyl ether monomer (**1**) was designed to form the most chemically labile polymer. As such, this sample tests both the limits of oxidative stability within this platform and also serves as inspiration for novel degradable materials.^[17]

Another divinyl ether main-chain functional monomer, containing a phosphocholine zwitterion (**2**), was synthesized to highlight the potential of hydrophilic and charged group incorporation into these polymers. Zwitterions have seen a recent surge in interest, not only as anti-fouling agents, but also for their biocompatible and anti-polyelectrolyte properties.^[18,19] Additionally, there are extremely limited accounts of main-chain zwitterions, so the incorporation of a main-chain phosphocholine demonstrated herein is one example of a new macromolecule enabled by TES polymerization. Finally, a diol functional group was selected to illustrate side-chain functionality with the interest of mimicking the properties of carbohydrates.^[20] In contrast to the previous two systems, the pendant diol was also incorporated through the dithiol monomer, in this case dithioerythritol (DTE; **3**), thus highlighting the versatility of this polymerization method and its ability to selectively incorporate functional groups into either monomer.

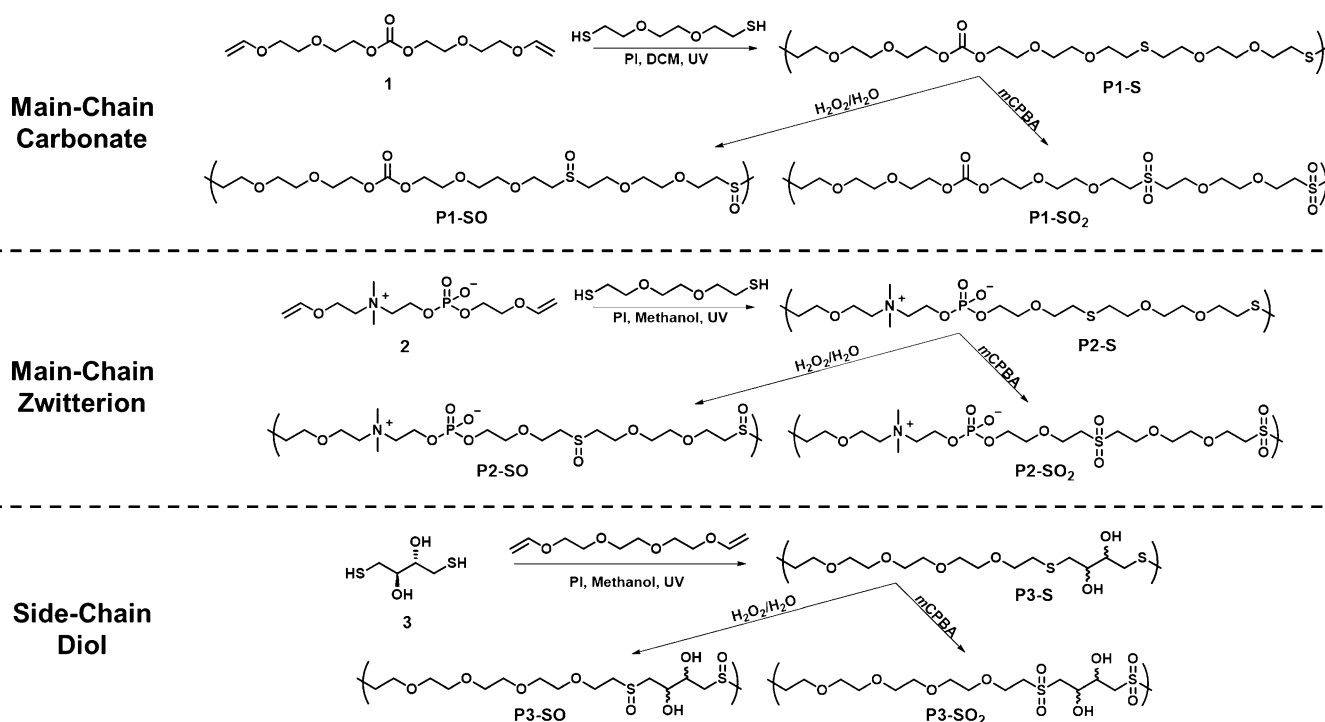
The divinyl ether monomers **1** and **2** were copolymerized with triethylene glycol dithiol, whereas **3** was copolymerized with triethylene glycol divinyl ether. These reactions yielded the corresponding polymers P1-S, P2-S, and P3-S. All polymerizations proceeded quantitatively as determined by

¹H NMR spectroscopy (see Figures S1, S2, and S5 in the Supporting Information). The ³¹P NMR spectrum of **2** showed a minute shift in the lone phosphodiester peak when compared to P2-S, thus indicating a very small change in chemical environment brought on by polymerization (see Figure S3). Polymers were purified of the residual photo-initiator by precipitation into diethyl ether, and subsequent gel permeation chromatography (GPC) to qualify molecular weight and dispersity (\mathcal{D}). P1-S was analyzed using DMF as a solvent, and showed a M_n value of 10.1 kg mol⁻¹ (Table 1). P2-S and P3-S were analyzed using TFE as the eluent, thus yielding estimated M_n values of 32.6 and 50.2 kg mol⁻¹, respectively (see Figures S7 and S8). In all cases, dispersity (\mathcal{D}) was less than the expected $\mathcal{D}=2$ (most probable distribution), and was attributed to the loss of low-molecular-weight material during precipitation.

Table 1: Molecular-weight properties of TES polymers.

| Polymer | M_n [kg mol ⁻¹] | M_w [kg mol ⁻¹] | \mathcal{D} |
|--------------------|-------------------------------|---|--------------------|
| P1-S | 10.1 ^[a] | 17.5 ^[a] | 1.7 ^[a] |
| P1-SO | 11.4 ^[a] | 19.2 ^[a] | 1.7 ^[a] |
| P1-SO ₂ | 16.7 ^[a] | 26.1 ^[a] | 1.6 ^[a] |
| P2-S | 32.6 ^[b] | 58.7 ^[b] / 11.2 ^[c] | 1.8 ^[b] |
| P2-SO | 20.3 ^[b] | 32.2 ^[b] / 16.0 ^[c] | 1.6 ^[b] |
| P2-SO ₂ | 14.6 ^[b] | 23.4 ^[b] / 12.3 ^[c] | 1.6 ^[b] |
| P3-S | 50.2 ^[b] | 67.1 ^[b] | 1.3 ^[b] |
| P3-SO | 43.3 ^[b] | 59.7 ^[b] | 1.4 ^[b] |
| P3-SO ₂ | 45.3 ^[b] | 68.8 ^[b] | 1.2 ^[b] |

[a] As measured by DMF GPC relative to PMMA standards. [b] As measured by TFE GPC relative to PMMA standards. [c] As determined using SEC-MALLS in aqueous 0.1 M NaCl.



Scheme 1. Synthetic approach to functional polymers through TES polymerization and subsequent oxidations.

Due to the nature of TES polymerization, resultant polymers contain thioether groups which are susceptible to oxidation, thus yielding either sulfoxide or sulfone functionalities which dramatically change the polarity of the material. This trait has been highlighted primarily in work describing the oxidative destabilization of thioether-containing micelles.^[21,22] We also demonstrated selective oxidation to either the sulfoxide or sulfone utilizing hydrogen peroxide or *m*CPBA, respectively.^[14] Herein, we show that this strategy is generalizable to thioethers containing an array of functional groups by generating the oxidized analogues of P1-S, P2-S, and P3-S, both as sulfoxides (PX-SO) and sulfones (PX-SO₂).

The conversion of thioethers into either sulfoxides or sulfones was monitored by both ¹H NMR spectroscopy and FTIR. As seen in Figure 2, protons α to the sulfur-centered

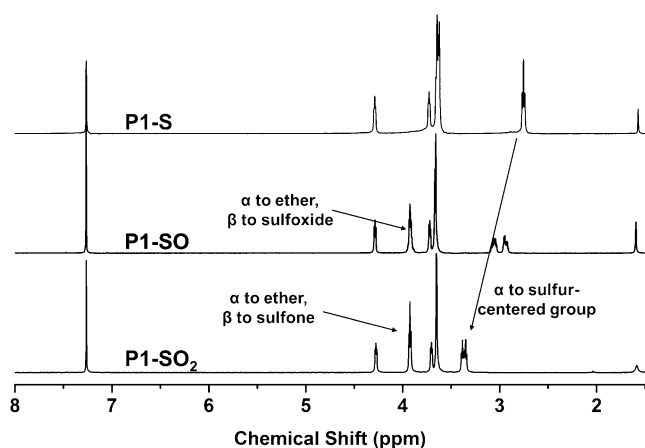


Figure 2. ¹H NMR (500 MHz, CDCl₃) spectroscopy describing the oxidation of the carbonate-containing polymer P1-S.

functional group moved progressively downfield as the level of oxidation increased. Each polymer sample (P2, P3 series in Figures S4–S6) showed only one sulfur group signal, that is, no over-oxidation to the sulfone exists in the sulfoxide polymers, and conversely no residual sulfoxides are present in the sulfone samples. This outcome was qualitatively supported by FTIR (see Figures S11–S13), where either a characteristic sulfoxide or sulfone stretch appeared near 1020 cm⁻¹ or from 1375 to 1325 cm⁻¹ respectively, for the appropriate polymers. The ³¹P NMR spectrum of the P2 series also showed a very minor upfield shift of the single phosphodiester peak as the oxidation level increased, by roughly $\delta = 0.1$ ppm (see Figure S3).

Tracking relative molecular weights of these polymers by GPC revealed no major changes in either molecular weight (MW) or \bar{M}_w associated with degradation. The \bar{M}_n value for the P1 series reported in Table 1 showed an increase from that of P1-S to P1-SO₂. However, examining the respective GPC curves in Figure 3 shows that the \bar{M}_n value is impacted by the changes in \bar{M}_w as \bar{M}_p remains essentially unchanged. The GPC curves show that the low-molecular-weight polymer is lost during the workup procedures following oxidation of the P1 series, but that polymer stability is maintained. This aspect thus is critical, as the main-chain carbonate polymer was the

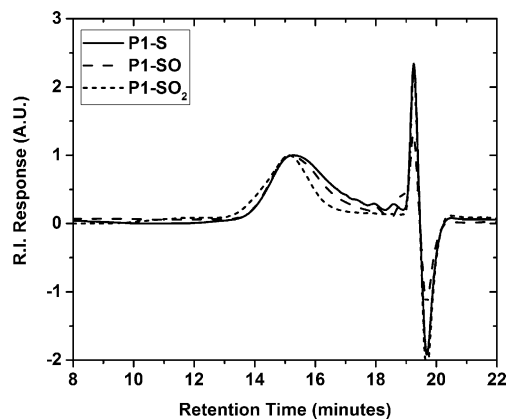


Figure 3. GPC traces in DMF of the P-1 oxidized series. The change in refractive index (R.I.) response at 19.5 minutes is due to air associated with sample injection.

most likely to decompose, thus demonstrating polymer fidelity throughout this oxidation process. Differential scanning calorimetry was also performed on the P1 series to demonstrate how polymer properties, in this case an increase in the T_g value, change with the oxidation state (see Figure S16). It is also important to note that for both the P1 and P3 series, the thioether polymers were water insoluble, whereas post-oxidation to either the sulfoxide or sulfone yielded completely water-soluble materials. This observation highlights the ability to modulate hydrophilicity and other properties of TES polymers.

The P2 and P3 series demonstrate qualitatively similar results. No degradation of the main backbone is observed following oxidation but the reported \bar{M}_n values change slightly. While the P2 series polymers show a progressive decrease in molecular weight as the degree of oxidation increases, the overall \bar{M}_w remained constant (see Figure S7). The P3 series had a slight decrease in the \bar{M}_n value for P3-SO and P3-SO₂ compared to P3-S (see Figure S8). To better understand these observed decreases in the \bar{M}_n value, the P2 series was analyzed by size-exclusion chromatography multi-angle laser light scattering (SEC-MALLS), and the P3 series was analyzed by DMF GPC. SEC-MALLS of the P2 polymers yielded comparable \bar{M}_w values for all three polymers, with P2-S having the lowest, opposite to the TFE GPC data (Table 1; see Figure S10). DMF GPC of the P3 polymers also showed opposing data, with an increase in the \bar{M}_n value for P3-SO₂ when compared to P3-S (see Figure S9). This data, in association with observed polymer stability through ¹H and ³¹P NMR data, as well as consistent polymer molecular weight distributions throughout oxidation, indicates that any observed change in molecular weight, post-oxidation, is almost certainly not associated with degradation. It is much more likely that the measured MW values are impacted by the solvent quality as the polymers are oxidized.

Through the step-growth polymerization of dithiols and divinyl ethers, we have demonstrated the synthesis of functional polymers with both main-chain (carbonate, phosphocholine zwitterion) and pendant (diol) groups. Using the

resulting thioether inherent to this polymerization, quantitative and selective oxidation reactions yielded either backbone sulfoxides or sulfones. We have also shown that either monomer, the dithiol or the divinyl ether, is capable of bearing the functional group of interest. Obvious extensions include polymers with increased functional-group density or mixed composition, where both monomers contain a tailored functional group. Even so, it should be kept in mind that the polymerization mechanism is step-growth. Different polymerization conditions systems will lead to different molecular weights and \bar{D} values near two. Regardless, with its functional group, water, and air tolerance, convenient synthesis, and accessibility to an understudied class of polymers, TES polymerization is a strong candidate for the next generation of advanced materials.

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